UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,388	11/28/2000	Jin Hong	7682-051-999	8169

20583 7590 06/15/2004

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,388	HONG ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-21* is/are pending in the application.

4a) Of the above claim(s) *9,13-16 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,8,10-12,17,18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *6-4-2004*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Currently, claims 7-21 are pending in the application.

2. In the prior action, mailed on September 24, 2003, claims 7-16 were pending, with claims 7, 8, and 10-12 rejected, and claims 9 and 13-16 withdrawn as to non-elected inventions. In the Response filed on March 24, 2004, the Applicant amended claims 7 and 11; and added new claims 17-21. Claims 7, 8, 10-12, 17, 18, 20, and 21 are under consideration to the extent that they read on the elected subject matter. Claims 9, 13-16, and 19 are withdrawn as to non-elected inventions.

3. Because this action raises issues not raised in the prior action, it is being made Non-Final.

Priority

4. It is noted that this application has been amended to claim benefit of priority to the prior Application No. 08316,439, filed September 30, 1994. Applicant's amendment of the specification to include the reference to the parent application as required by 35 U.S.C. § 120 is noted.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **(Prior Rejection- Maintained)** Claim 12 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim reads on a vaccine comprising a genetically manipulated virus of the paramyxoviridae family, wherein the genetic manipulation comprises any insertion, deletion, or substitution, and may also, optionally, comprise a heterologous sequence. The viruses of the paramyoviridae family are further identified in the dependent claims as including the parainfluenza virus (PIV) and RSV. Thus, while the claims are broadly drawn to vaccines against any non-segmented, negative-stranded RNA virus, or to any paraxymovirus, the contents of the specification, and the dependant claims clearly indicate that the presently claimed invention is focused on vaccines against RSV.

The Applicant traverses the rejection by asserting that the teachings of the specification provide adequate information to enable those in the art to make and use the claimed inventions. In particular, the Applicant challenges the assertion in the rejection that the Applicant has not disclosed or enabled those in the art to use the claimed RSV variants as vaccine antigens. In support of their assertion, the Applicant notes a post-filing publication by the inventors shoeing vaccine efficacy of a RSV variant in African Green Monkeys. The Applicant further argues that among the teachings referred to by the Examiner to demonstrate unpredictability, one of the obstacles presented refers not to attenuated virus, but to formalin inactivated virus, and one of the references indicates that the use of genetically engineered RSV as a significant advance in

vaccine development, and provides a positive outlook for their use. These arguments in traversal are not found persuasive.

The Applicant's first argument in traversal is that the Applicant, in the 2001 Cheng et al. article (Virology 283:59-68), has demonstrated the efficacy of a particular recombinant RSV to induce a protective response in African Green Monkeys. However, while the use of accepted models for a disease may be predictive of human responses to a potential therapy for the disease, such is not presently the case with respect to RSV infections. That is, the art does not show an acceptance of a particular animal model as predictive of human responses to RSV vaccines. In specific, while the art is aware of the mouse, cotton rat, and Green monkey models of RSV, those in the art have nonetheless failed to successfully vaccinate against RSV infection. See e.g., Dudas et al., Clin Microbiol Rev 11(3): 430-39, esp. page 432 (indicating that although animal models provide information regarding the potential vaccines, the vaccines so identified have not been established as protective in humans). See also, Prince et al., J Virol 74(22): 10287-92; and, more recently, Tang et al., J Virol 77(20): 10819-28. Each of the Prince and Tang articles indicates that, to date, there are no effective anti-RSV vaccines for humans. Rather, while numerous vaccine candidates have been tested, several challenges have arisen in the development of such vaccines which have prevented the identification of one that is safe and effective in people. In view of the above, while the Applicant may have provided an enabling disclosure for the making of attenuated RSV, the Applicant has not provided sufficient information to allow those in the art to use such virus as RSV vaccines without undue experimentation. This is because the Applicant has not provided those in the art with sufficient information such that they would be able to easily make and identify virus that would be useful

for the safe induction of a protective immune response in humans. The first argument in traverse is therefore not found persuasive.

The Applicant's second argument in traversal appears to be asserting that the Examiner has not established the unpredictability of the art surrounding RSV development. However, while the Applicant is correct in their assertion regarding the teachings of Murphy on page 17 of that article, and the suggestion of Kahn regarding the value of recombinant RSV technology, these teachings do not demonstrate a lack of unpredictability in the art. Murphy demonstrates that those in the art have been aware of the difficulties in RSV vaccine development for some time. Yet, while Kahn recognizes the value of recombinant technology to RSV vaccine development, the reference also clearly indicates that the difficulties facing those in the art of developing such vaccines are ongoing. See, page 257 (stating that the development of RSV vaccines "faces many obstacles," thereby indicating that, despite the advances referred to later in the article, the obstacles have not been overcome). Further evidence of ongoing challenges to RSV vaccine development may also be found in the Prince and Tang references cited above. In view of these teachings by the art, the Applicant's assertions that there is no unpredictability in the art, and that the current application is therefore enabling for RSV vaccines, are not found persuasive. The rejection is therefore maintained for the reasons above, and for the reasons of record.

7. **(New Rejection)** Claims 7, 8, 10-12, 17, 18, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims have been amended to read on genetically manipulated replication competent infectious RSV comprising any insertion or deletion, or any insertion, substitution, or deletion of an entire open reading frame (ORF).

Thus, the claims are broadly drawn to any replication competent, infectious RSV comprising any addition or deletion; or any addition, substitution, or deletion of an entire open reading frame (ORF). However, while the Applicant has provided some examples of rearrangement or deletion of the ORFs, and some examples of other modifications that may be made to the genome, the Applicant has not provided sufficient information such that those in the art would be able to produce virus with the required functions to the full extent of the claims. The examples provided by the Applicant are not commensurate in scope with the breadth of the genetic manipulations permitted by the claims.

The specification in the present case provides some examples of substitutions that result in RSV with various affects on their replicative phenotype. See, and pages 58-59 (discussing substitution mutations to the L protein). These examples demonstrate that, while some substitutions in the L gene lead to attenuated phenotypes, other resulted in no change, therefore indicating that the viral genome is tolerant of some manipulation; certain mutations resulted in phenotypes which the Applicant states "are not expected to be viable." Thus, the Applicant has demonstrated that the effect of any particular substitution (and thus deletion or addition) is unpredictable. I.e., the Applicant was unable to determine prior to making the substations what, if any, effect a particular substitution would have on the viral activity.

The teachings in the art of protein modification support the indications of unpredictability present in the present application. For example, Bowie (Science 247: 1306-10) teaches that, although proteins are generally tolerant to substitutions, the effect that substitution of any particular residue will have on a protein's function is dependant on the association of that residue to the protein's structure and function. The reference indicates that a particular residue may be open to any substitution, or may accept only conservative or no substitutions without an effect on protein function. Thus, the reference teaches that the art of protein modification is unpredictable. Further, while the reference indicates that some of the unpredictability may be resolved with teachings as to the relationship between the residue to be mutated and the protein structure and function, no teachings regarding the essential residues or structures of the RSV proteins have been provided in the present application. Thus, based on the teachings in the art and in the specification, the effects of any particular mutation to the RSV genome, and use of such mutation to effect attenuation of RSV, are clearly complex and unpredictable arts.

While the Applicant has provided some teachings with respect to viral mutations that may be made while retaining viral function, the Applicant has not provided sufficient information such that any addition, substitution, or deletion to the viral genome may be made resulting in an RSV with the desired functional characteristics. The Applicant has not provided sufficient information such that those in the art could may any such mutation to the genome with the expectation that they would have a replication competent infectious virus. Thus, in order to practice the claimed invention their full scope, those in the art would be required to make, and then test the effects of every possible insertion, deletion, or substitution to the viral genome. Therefore, given the breadth of the claims, the unpredictability of the art, and the limited

guidance in the specification, the Applicant has not provided sufficient information such that those in the art may practice the full scope of the claimed inventions without undue experimentation.

Claim 21 further limits the claimed inventions to virus wherein the M2 open reading frame has been added, substituted, or deleted. The Applicant argues that support for this embodiment may be found in pages 45-48 of the current application. It is noted that the experimental data on these pages does not include the making of a working model of an RSV comprising a deletion or substitution of the M2 ORF. Further, the conclusion drawn by the Applicant from the data presented in the pages has not been accepted by the art. See e.g., Collins et al. Virology 259: 251-55 (reference CQ in the June 2003 IDS). The Collins article both provides reasons why the Applicant's conclusion that the M-2 ORF, and in particular the M2-1 protein, is not required may have inadequate scientific foundation; and (on page 254) indicates that the only way to determine if an operable virus may be made without the M2-1 protein is to make a virus wherein the M2 ORF has been deleted from the viral genome. Thus, the art demonstrates both complexity and uncertainty with respect to the invention of claim 21. In view of this, and the lack of working examples demonstrating that those in the art would be able to make and use RSV lacking the M2 ORF, the Applicant has not provided adequate information to enable those in the art to make and use the claimed invention without undue experimentation.

8. **(New Rejection)** Claims 7, 8, 10-12, 17, 18, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been described above. They read on a genus of inventions comprising any RSV virus with any of the genetic manipulations described above wherein the virus also has the functionally activities of being replication competent and infectious.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present application, the Applicant has provided a limited number of examples of the claimed genus, and has provided little guidance as to what structures of the viral genome are necessary for the virus to perform the required functions. The limited number of examples do not provide sufficient support for the breadth of genetic variations permitted by the claims. Further, the application does not provide information as to the proteins, or residues or structures within

the proteins, that are required for the virus to be replication competent and infectious. Thus, the application does not provide necessary information regarding the structures required in order for the virus to have the claimed functions (i.e., the Applicant has not provided structures that correlate with the desired functions). In view of the above, and because the examples provided do not provide written descriptive support sufficient to reflect the variation within the claimed genus of inventions, the claims are rejected for lacking written description.

9. **(New Rejection)** Claims 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim reads on the claimed genus of RSV virus wherein the viral genome has been manipulated such that the M-2 open reading frame has been substituted for another sequence, or deleted from the genome.

The written description requirements for a genus of inventions have been described above. In addition, it is noted that even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus where there is unpredictability in the art regarding the operation of specific embodiments. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43

USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, where there is uncertainty in the art regarding the operability of individual species, an Applicant may be found to have provided inadequate support for a claimed genus even if they have provided sufficient information such that the description requirement would have been met in the absence of the uncertainty.

In the present case, the Applicant has not provided any working examples of RSV with the claimed functional requirements wherein the M-2 protein has been deleted or substituted out of the viral genome. Further, while the Applicant asserts that the M-2 protein is not essential to the indicated functionalities, the teachings in the art demonstrate uncertainty as to whether or not this ORF is required. For example, the teachings of the present application with reference to the M-2 ORF were presented in a 1998 article by Jin et al. (Virology 251:206-214 (1998)- reference DA in the June 2003 IDS). The conclusions formed by this article that the M-2 protein is not required for viral replication were challenged by a later reference by Collins et al. Virology 259: 251-55 (reference CQ in the June 2003 IDS). The Collins article provides reasons why the Applicant's conclusion that the M-2 ORF, and in particular the M2-1 protein, is not required may have inadequate scientific foundation. The reference further indicates that the only way to determine if an operable virus may be made without the M2-1 protein is to make a virus wherein the M2 ORF has been deleted from the viral genome. Page 254. Thus, the Applicant has provided inadequate written descriptive support for claim 21 in view of the uncertainty in the art regarding the operability of RSV lacking ht eM2 ORF. For these reasons, and for the reasons indicated above with respect to claims 7, 8, 10-12, 17, 18, and 20, claim 21 is rejected for lack of written description support.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. **(Prior Rejection- Withdrawn)** Claims 7, 10, and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Gharpure et al., J Virol 3(4): 414-21 (of record in the March 2, 2001 IDS). These claims have been amended to read on genetically manipulated RSV virus wherein the viral genome comprises a modification that either an insertion or a deletion. Additionally, new claims have been added that require "an addition, substitution, or deletion of an open reading frame encoding a viral gene product" (i.e. requiring that an entire ORF be inserted, deleted, or substituted). See, Response page 10 (describing language of claim 18). In view of the amendment of the claim language, the rejection is withdrawn.

12. **(Prior Rejection- Withdrawn)** Claims 7, 8, and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Park et al., PNAS 88: 5537-41 (of record in the March 2, 2001 IDS). These claims have been amended such that they now require that the claimed virus is replication competent. In view of the amendment, and the arguments presented therewith, the rejection is withdrawn.

13. **(Prior Rejection- Withdrawn)** Claims 7, 10, and 11 were rejected under 35 U.S.C. 102(a) as being anticipated by Crowe et al., Vaccine 12(8): 691-99 (June 1994- of record in the IDS filed on March 2, 2001). IDS). These claims have been amended to read on genetically manipulated RSV virus wherein the viral genome comprises a modification that either an insertion or a deletion. Because Crowe does not teach RSV comprising an addition or deletion, the rejection is withdrawn.

14. **(Prior Rejection- Withdrawn)** Claims 7, 8, 10, and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Collins et al., Virology 195: 252-56 (Collins I, July 1993- of record in the IDS filed on March 2, 2001) or by Collins et al., PNAS 88: 9663-67 (Collins II, also of record in the March 2001, IDS). The claims, and the amendments thereto, have described above. In view of the amendments to the claim, the rejection is withdrawn.

15. **(Prior Rejection- Maintained)** Claim 11 was rejected under 35 U.S.C. 102(a) as being anticipated by either of Conzelmann et al, J Virol. 68(2): 713-19, or Schnell et al., The EMBO Journal 13(18): 4195-4203 (September 15, 1994- of record in the March 2, 2001 IDS). The claim describes genetically manipulated infections, non-segmented, negative-stranded RNA virus, the genome of which comprises a modification that is one of an insertion, or deletion. Each of the two cited references is directed to negative stranded RNA viruses other than RSV.

The Applicant traverses the rejection on the basis of the assertions in the Declaration by David Clark (filed March 24, 2004) that the Applicant was in possession of the claimed invention prior to the publication dates of these references. However, the assertions of the Clark Declaration are limited to embodiments wherein the virus is RSV. The claims are not so limited,

and the references are directed to such other embodiments. Because the affidavit is not fully commensurate with the rejected claim, and does not demonstrate possession of the virus disclosed by the cited references, the Clark Declaration filed under 37 CFR 1.131 has been considered, but is ineffective to overcome anticipation rejection over the Schnell and Conzelmann references.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 6/13/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600